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Computational Molecular Biology 2024, Vol.14, No.5, 220-228
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Review and Progress **Open Access**

Integrative Approaches in Computational Genomics: Combining Omics Data to Study Gene Evolution

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Computational Molecular Biology, 2024, Vol.14, No.5 doi: 10.5376/cmb.2024.14.0025
Received: 23 Aug., 2024
Accepted: 25 Sep., 2024
Published: 30 Oct., 2024

Preferred citation for this article:
Liu H.W., 2024, Integrative approaches in computational genomics: combining omics data to study gene evolution, Computational Molecular Biology, 14(5): 220-228 (doi: 10.5376/cmb.2024.14.0025)

Abstract This study explores integrative approaches in computational genomics that combine multi-omics data to study gene evolution. It provides a detailed analysis of the key components of genomics, transcriptomics, proteomics, and epigenomics, clarifying their roles in gene evolution research. Furthermore, it discusses computational techniques such as network-based methods, machine learning, and gene set analysis, which enhance the integration and interpretation of multi-omics data. With the advancement of high-throughput technologies, multi-omics integration has become a vital approach to understanding the complexity of gene evolution, as it offers a comprehensive perspective on how changes in the genome, transcriptome, proteome, and epigenome drive evolutionary processes. Through case studies in agriculture, medicine, and microbial evolution, this study emphasizes the practical applications of multi-omics integration, reveals the molecular mechanisms behind gene evolution, and provides guidance for future research and applications across various fields.

Keywords Multi-omics integration; Gene evolution; Computational genomics; Machine learning; Epigenomics

1 Introduction

Gene evolution is a fundamental aspect of biology that provides insights into the mechanisms driving diversity and adaptation in living organisms. Understanding gene evolution helps elucidate the origins of genetic variation, the development of new functions, and the evolutionary pressures shaping genomes over time. This knowledge is crucial for various applications, including evolutionary biology, medicine, and biotechnology. By studying gene evolution, researchers can identify conserved genetic elements, understand the basis of genetic diseases, and develop strategies for genetic engineering and synthetic biology (Qin et al., 2016; Agamah et al., 2022).

Computational genomics leverages advanced computational techniques to analyze and interpret complex genomic data. With the advent of high-throughput technologies, vast amounts of data from different omics layers—such as genomics, transcriptomics, proteomics, and metabolomics—are generated. Integrating these multi-omics datasets is essential to gain a comprehensive understanding of biological systems and their regulatory mechanisms (Demirel et al., 2021; Wörheide et al., 2021). Multi-omics integration involves combining data from various sources to highlight the interrelationships between biomolecules and their functions, providing a holistic view of cellular processes (Subramanian et al., 2020).

This study will explore integrative approaches in computational genomics that combine multi-omics data to study gene evolution. It aims to identify and evaluate current methods and tools used for multi-omics data integration, including network-based approaches, machine learning techniques, and gene set analysis methods, to promote comprehensive analysis of multi-omics data. The study will discuss the application of these integrative methods in understanding gene evolution, with a focus on how they can be used to investigate gene regulation, identify evolutionarily conserved elements, and uncover the molecular mechanisms driving gene evolution. Through the application of multi-omics data integration techniques, this study aims to provide a more comprehensive and deeper understanding of gene evolution, while offering guidance for future research and practical applications.

2 Genomics and Gene Evolution Studies

2.1 Genomic structural variations

Genomic structural variations, including insertions, deletions, duplications, and translocations, play a significant role in gene evolution by altering gene function and regulation. These variations can lead to phenotypic diversity and adaptation in populations (Ding, 2024). Integrative approaches that combine various omics data, such as genomics, transcriptomics, and proteomics, are essential for understanding the impact of these structural variations on gene function and evolution. For instance, the integration of high-throughput phenotyping and multi-omics data in canola has revealed prime candidate genes associated with metabolic and vegetative growth variations, highlighting the importance of structural variations in plant trait evolution (Figure 1) (Knoch et al., 2023).

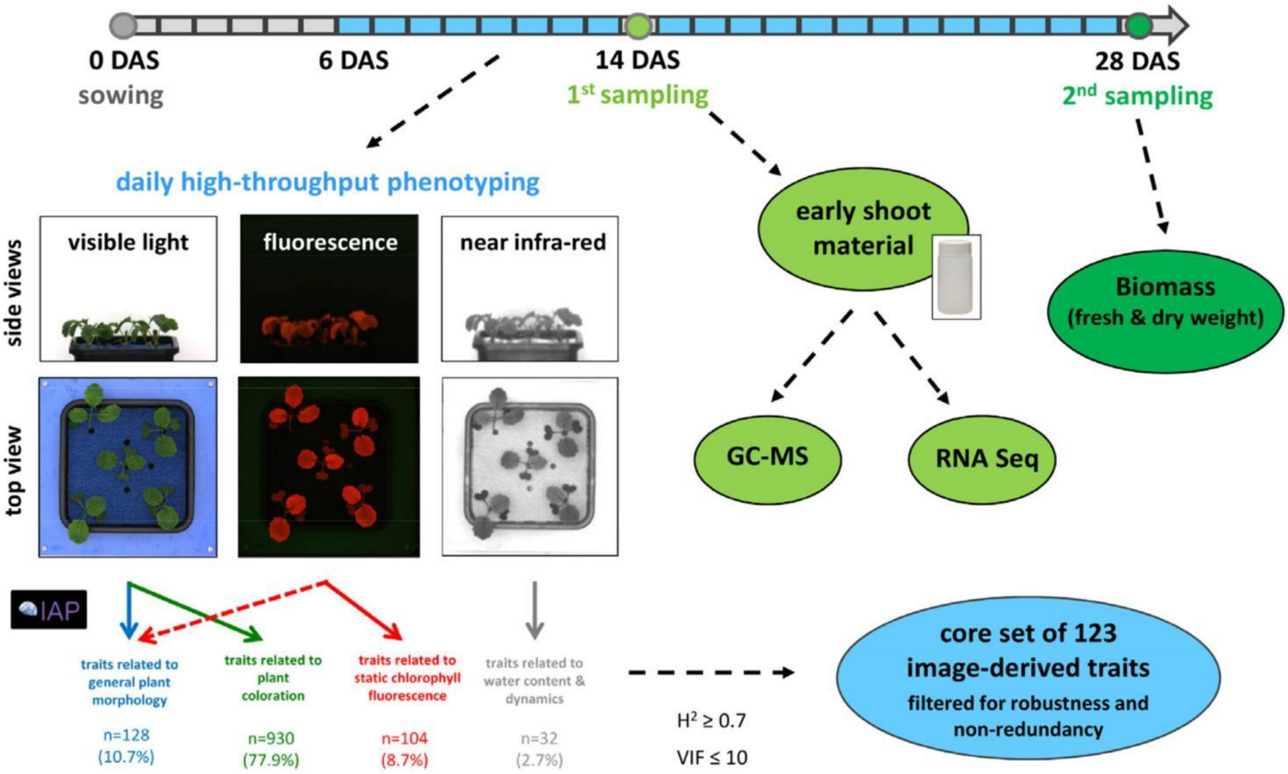

Figure 1 Experimental workflow to generate the phenotyping and omics data (Adopted from Knoch et al., 2023)

2.2 Genome-wide association studies (GWAS)

Genome-wide association studies (GWAS) have been instrumental in identifying genetic loci associated with complex traits and diseases. However, the interpretation of these loci often remains challenging due to their location in noncoding regions and the complexity of linkage disequilibrium (LD). Integrative approaches that incorporate functional annotations and multi-omics data can enhance the power and resolution of GWAS. For example, a scalable Bayesian method has been developed to integrate functional information into GWAS, improving the identification of causal variants and underlying biological mechanisms (Yang et al., 2017). Multi-omics studies have been used to interpret GWAS findings, providing insights into the pathogenesis of complex diseases and their causative factors (Sun and Hu, 2016; Akiyama, 2020).

2.3 Comparative genomics

Comparative genomics involves the analysis of genomic features across different species to understand evolutionary relationships and the conservation of genetic elements. Integrative approaches that combine comparative genomics with other omics data can provide a comprehensive view of gene evolution. For instance, integrative multi-omics analyses have been used to identify candidate genes for metabolic and vegetative growth variations in canola, demonstrating the power of combining genomic, transcriptomic, and metabolomic data. Moreover, integrative methods have been applied to transcriptome-wide association studies (TWAS) to identify gene-trait associations, leveraging multi-omics data to prioritize distal variants and uncover complex regulatory mechanisms (Gusev et al., 2015; Bhattacharya et al., 2020).

3 Transcriptomics and Evolution of Gene Regulation

3.1 Evolution of gene expression patterns

The evolution of gene expression patterns is a critical area of study in understanding how organisms adapt and evolve. Integrative omics approaches, particularly those combining transcriptomics with other data types, have provided significant insights into these patterns. For instance, the integration of transcriptome and proteome profiling has revealed the dynamic nature of gene regulation across different cellular states and conditions. This unified analysis helps in deciphering gene regulations and discovering disease markers and drug targets (Kumar et al., 2016). Bayesian inference models have been employed to quantify and compare gene expression across different conditions, providing a probabilistic framework to understand the evolution of gene expression (Jiménez et al., 2021).

3.2 Evolution of non-coding RNAs

Non-coding RNAs (ncRNAs) play a crucial role in gene regulation and their evolutionary patterns are essential for understanding complex regulatory networks. Integrative single-cell analysis has highlighted the importance of ncRNAs in cellular modalities and their role in gene expression regulation. By profiling genetic, epigenetic, and transcriptomic data at single-cell resolution, researchers can uncover the contributions of ncRNAs to gene regulatory mechanisms (Stuart and Satija, 2019; Campbell et al., 2020). Furthermore, integrative pathway enrichment analysis has identified ncRNAs as key players in various biological pathways, emphasizing their evolutionary significance in gene regulation.

3.3 Transcriptomic changes under environmental stress

Environmental stress induces significant transcriptomic changes, which are crucial for the survival and adaptation of organisms. Integrative omics studies have been pivotal in understanding these changes. For example, the integration of transcriptomic, proteomic, and metabolomic data has provided a comprehensive view of how plants respond to abiotic stresses such as salinity, drought, and toxic conditions. These studies have identified key genes and proteins involved in stress responses, offering insights into the molecular mechanisms underlying plant adaptation to environmental stress (Wang et al., 2019). Integrative approaches combining multiple omics data have been used to study the impact of environmental stress on gene expression patterns, revealing the complex interplay between different molecular layers (Qin et al., 2016).

4 Proteomics and Functional Evolution

4.1 Evolution of protein families

The evolution of protein families is a critical aspect of understanding functional genomics. Integrative multi-omics approaches have significantly advanced our ability to study protein families by combining data from various omics layers, such as genomics, transcriptomics, and proteomics. These approaches allow for a comprehensive analysis of protein evolution, revealing how genetic variations and environmental factors influence protein function and interaction networks. For instance, the integration of proteomics with other omics data has been shown to provide deeper insights into the functional roles of proteins and their evolutionary trajectories (Demirel et al., 2021).

4.2 Protein modifications and functional regulation

Protein modifications, particularly post-translational modifications (PTMs), play a crucial role in regulating protein function and activity. The interplay between metabolites and PTMs is a key area of study in integrative proteomics. Metabolites can act as regulators of PTMs, which in turn affect enzyme activity and metabolic pathways. This dynamic relationship underscores the importance of integrating proteomics with metabolomics to understand the regulatory mechanisms at play. Recent studies have highlighted the potential of multi-omics approaches to uncover the complex feedback loops between metabolites and PTMs, providing new avenues for understanding disease mechanisms and identifying biomarkers (Blum et al., 2018; Nalbantoğlu and Karadag, 2021).

4.3 Evolution of protein interaction networks

The evolution of protein interaction networks is essential for understanding the functional organization of cellular processes. Integrative multi-omics approaches have enabled the construction of comprehensive protein-protein interaction (PPI) networks by combining data from various omics sources. These networks provide a global view of the molecular interactions within a cell, revealing how proteins interact with each other and with other biomolecules. Network-based methods have been particularly effective in identifying key nodes and subnetworks that are critical for cellular function and disease progression (Randhawa and Pathania, 2020; Agamah et al., 2022). By integrating proteomics with other omics data, researchers can gain a more detailed understanding of the evolutionary changes in PPI networks and their implications for cellular function.

5 Epigenomics and Its Role in Gene Evolution

5.1 Role of DNA methylation in evolution

DNA methylation is a crucial epigenetic modification that influences gene expression by adding methyl groups to DNA, typically at CpG sites. This modification can lead to gene silencing and is essential for various biological processes, including development, differentiation, and disease. In the context of evolution, DNA methylation patterns can be inherited and modified in response to environmental changes, thereby contributing to evolutionary adaptation. For instance, studies have shown that DNA methylation can capture and mediate the effects of genetic and environmental risk factors on complex diseases, highlighting its role in evolutionary processes. The progressive loss of DNA methylation in heterochromatic regions during T cell differentiation underscores its importance in cellular memory and lineage specification (Durek et al., 2016).

5.2 Evolutionary function of histone modifications

Histone modifications, such as methylation, acetylation, and phosphorylation, play a pivotal role in regulating chromatin structure and gene expression. These modifications can either activate or repress gene transcription, depending on the specific histone mark and its location. The dynamic nature of histone modifications allows for rapid responses to environmental stimuli, which can be crucial for evolutionary adaptation. For example, integrative analyses of histone modifications in cancer cells have revealed distinct chromatin states associated with gene activity and inactivity, suggesting that histone modifications contribute to the regulation of gene expression in response to evolutionary pressures. Furthermore, single-cell profiling of histone modifications has identified cell-type-specific regulatory mechanisms, emphasizing the role of histone modifications in the evolution of complex tissues (Zhu et al., 2021).

5.3 Epigenetic memory and environmental adaptation

5.3.1 Mechanisms of epigenetic memory in response to environmental stimuli

Epigenetic memory refers to the heritable changes in gene expression that do not involve alterations in the DNA sequence. This memory can be established through various mechanisms, including DNA methylation and histone modifications. Environmental stimuli, such as stress or changes in diet, can induce epigenetic changes that are maintained across cell divisions and potentially across generations. For instance, the epigenetic landscape of chronic lymphocytic leukemia (CLL) cells shows disease-specific patterns of DNA methylation and histone modifications, which are imprints of the cellular origin and proliferative history, indicating a form of epigenetic memory (Kulis and Martín-Subero, 2022; Mason, 2024). The integrative analysis of epigenomic data has identified regulatory elements and transcription factor networks that mediate gene deregulation in response to environmental changes.

5.3.2 Role of epigenetic inheritance in long-term adaptation

Epigenetic inheritance allows for the transmission of epigenetic marks from one generation to the next, providing a mechanism for long-term adaptation to environmental changes. This form of inheritance can influence phenotypic variation and evolutionary fitness without altering the underlying genetic code. For example, DNA methylation patterns can be stably inherited and influence gene expression in offspring, thereby contributing to long-term adaptation (Teschendorff and Relton, 2017). The study of epigenetic modifications in pulmonary diseases has also highlighted the potential for epigenetic marks to serve as noninvasive biomarkers, reflecting long-term environmental exposures and their impact on disease susceptibility (Benincasa et al., 2020).

5.3.3 Epigenetic regulation of stress-response genes

Stress-response genes are often regulated by epigenetic mechanisms, allowing organisms to adapt to changing environmental conditions. DNA methylation and histone modifications can modulate the expression of these genes, enabling a rapid and reversible response to stress. For instance, the silencing of transgene expression in mammalian cells through DNA methylation and histone modifications demonstrates the role of these epigenetic marks in controlling gene expression in response to stress. Moreover, the integrative analysis of epigenomic data has identified stress-response genes that are regulated by specific histone modifications, further emphasizing the importance of epigenetic regulation in environmental adaptation (Gopi and Kidder, 2021).

6 Applications of Integrative Omics Data in Evolution Studies

6.1 Gene evolution and breeding applications in agriculture

Integrative omics approaches have significantly advanced our understanding of gene evolution and breeding in agriculture. By combining genomics, transcriptomics, proteomics, metabolomics, and phenomics, researchers can elucidate the complex interactions between genes and their phenotypic expressions under various environmental conditions. For instance, multi-omics technologies have been successfully applied to crops such as wheat, soybean, tomato, barley, maize, millet, cotton, Medicago truncatula, and rice to study growth, senescence, yield, and responses to biotic and abiotic stresses (Yang et al., 2021). These integrative approaches enable the identification of key genetic traits and molecular networks that can be targeted for crop improvement, ultimately enhancing agricultural productivity and resilience.

6.2 Evolutionary studies in medicine

In the field of medicine, integrative omics data have been pivotal in understanding the evolutionary aspects of diseases and their treatment. By integrating genomics, transcriptomics, proteomics, and metabolomics, researchers can gain a comprehensive view of the molecular mechanisms underlying various diseases. This holistic approach has been instrumental in identifying biomarkers, disease subtypes, and molecular drivers of diseases, which are crucial for the development of personalized medicine (Karczewski and Snyder, 2018; Reel et al., 2021). For example, integrative omics has been used to study the etiology and treatment of complex diseases such as cancer and transplant biology, providing insights that are not possible with single-omics approaches.

6.3 Microbial evolution and biotechnology

Integrative omics approaches have also been applied to study microbial evolution and biotechnology. By combining multiple omics data, researchers can explore the genetic and metabolic networks of microorganisms, leading to a better understanding of their evolutionary processes and potential biotechnological applications. For instance, network-based integrative approaches have been used to represent interactions between different omics layers in microorganisms, providing insights into their molecular wiring and evolutionary dynamics (Agamah et al., 2022). These studies have implications for biotechnology, where understanding microbial evolution can lead to the development of new bioproducts and bioprocesses.

7 Case Studies

7.1 Multi-omics analysis of human gene evolution

The integration of multi-omics data has significantly advanced our understanding of human gene evolution. By combining data from genomics, proteomics, and metabolomics, researchers can gain a comprehensive view of the molecular mechanisms underlying gene evolution. Machine learning approaches have been particularly effective in this domain, enabling the discovery of new biomarkers and providing insights into disease prediction and patient stratification. Network-based integrative approaches have also been instrumental, allowing for the representation of interactions between different omics layers, which can reflect the molecular wiring in cells and identify key nodes and subnetworks involved in human gene evolution (Figure 2) (Agamah et al., 2022).

7.2 Integrative omics study of coral adaptation evolution

Coral adaptation to changing environmental conditions is a complex process that can be better understood through integrative omics studies. By utilizing high-throughput techniques and multi-omics data, researchers can highlight the interrelationships of biomolecules and their functions in coral species. Tools and methods developed for multi-omics data integration have been applied to study coral adaptation, providing insights into the molecular drivers of physiological and pathological mechanisms in these organisms (Subramanian et al., 2020). The use of cloud computing and containerization has further facilitated the scaling and linking of functional services designed for various purposes, making it easier to perform integrative analyses of coral adaptation evolution (Augustyn et al, 2021).

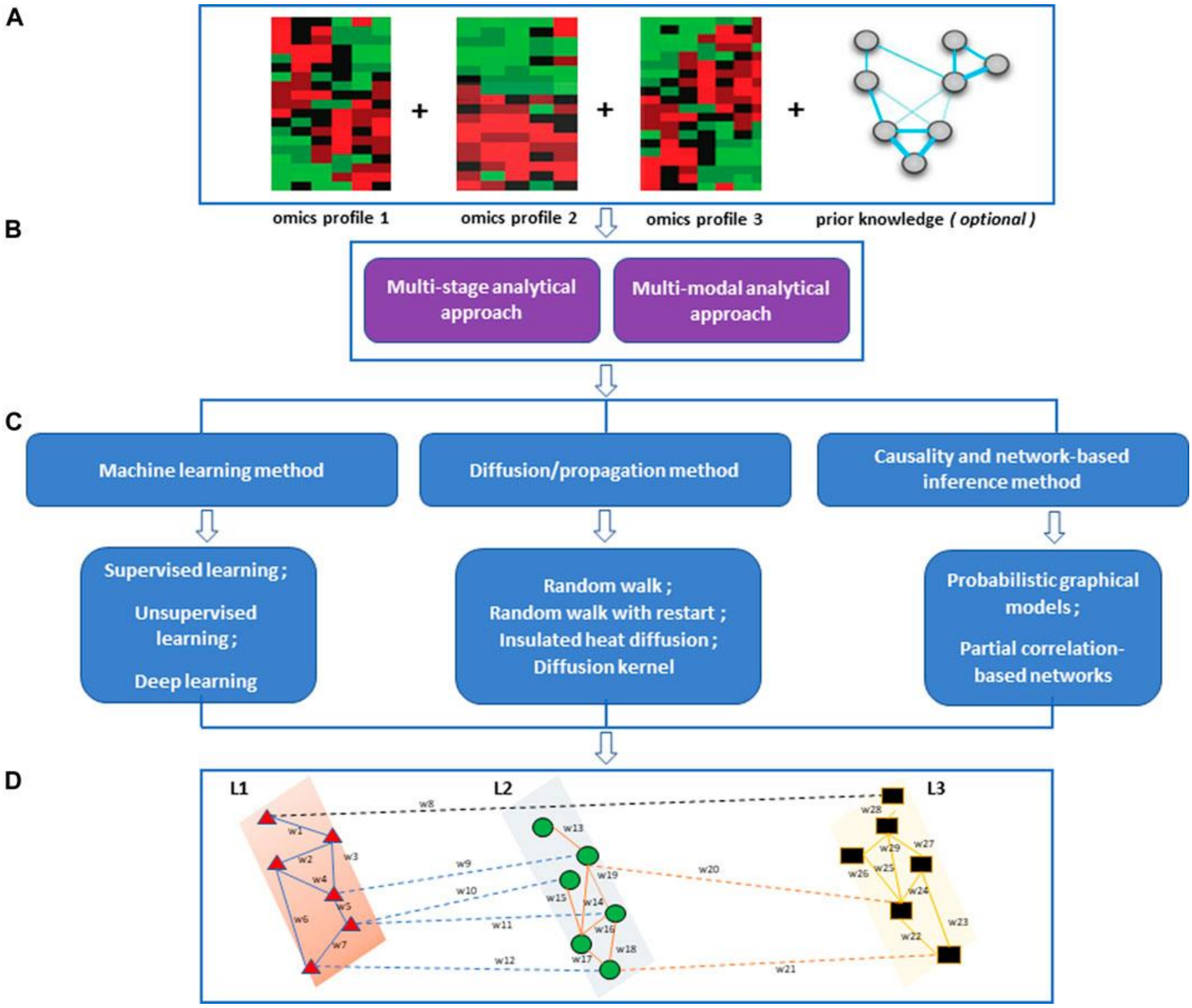

Figure 2 An overview of the multi-omics integration approach and the methods for network-based integration. (A) Processed omics data and prior knowledge for integrative analysis. (B) An integrative multi-omics approach that could be implemented. (C) Integrative network-based methods (D) Multi-layered network showing intra-layer interaction (solid lines) and crosstalk (dashed lines) across different layers (L1, L2, L3) (Adopted from Agamah et al., 2022)

7.3 Gene evolution study on stress-resistance traits in soybean

The study of stress-resistance traits in soybean has benefited from the integrative analysis of multi-omics data. By employing a powerful framework that manages and analyzes heterogeneous omics data, researchers have been able to carry out comprehensive integrative analyses. For instance, the mixOmics package for R software has been used to integrate phenomics, metabolomics, cell wall proteomics, and transcriptomics data to study the cell wall plasticity of plants exposed to sub-optimal temperature growth conditions (Duruflé et al., 2020). This approach has enabled the identification of novel conclusions on the biological system, which would not have been possible using standard statistical methods. The methodologies presented in these studies can be applied to various organisms and biological questions, making them highly versatile for studying gene evolution in stress-resistant traits.

8 Concluding Remarks

Integrative approaches in computational genomics have significantly advanced our understanding of gene evolution by combining various omics data. The integration of multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, has provided a more comprehensive view of the complex regulatory systems governing gene functions. Studies have demonstrated that integrative OMICs approaches are essential for elucidating the molecular basis of biological regulatory mechanisms, as they offer a precise and effective way to study gene regulations. Various methods, such as Bayesian clustering, matrix factorization, and network-based approaches, have been evaluated for their effectiveness in integrating multi-omics data, showing that integrative methods generally outperform non-integrative ones in uncovering coordinated cellular processes.

Machine learning techniques have also been pivotal in multi-omics data analysis, enabling the discovery of new biomarkers and aiding in disease prediction and patient stratification. Tools like mixOmics have been developed to facilitate the multivariate analysis of biological datasets, providing methods for data exploration, dimension reduction, and visualization. Additionally, pathway enrichment analysis methods, such as ActivePathways, have been used to identify significantly enriched pathways across multiple datasets, further enhancing our understanding of gene evolution and disease mechanisms.

The findings from these integrative approaches highlight several implications for future research. Firstly, there is a need for the development of more sophisticated bioinformatics tools that can handle the high dimensionality and heterogeneity of multi-omics data. Future research should focus on improving the accuracy and efficiency of these tools to better integrate and interpret complex datasets. Moreover, the application of cloud computing and containerization technologies presents a promising avenue for scaling and optimizing multi-omics data analysis pipelines. These technologies can facilitate the orchestration of complex analysis workflows, making it easier to manage and process large-scale datasets. Another important area for future research is the standardization of data integration protocols. The lack of universal analysis protocols has been a significant challenge, and establishing standardized methods will be crucial for ensuring reproducibility and comparability of results across different studies. Finally, there is a need for more comprehensive comparative studies to assess the performance and biological value of different integrative methods. Such studies will help identify the most effective approaches for specific research questions and guide the development of new methodologies.

Acknowledgments

We would like to express our gratitude to the two reviewing experts for their reading and revision suggestions, which have contributed to the improvement of our research.

Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Agamah F.E., Bayjanov J.R., Niehues A., Njoku K.F., Skelton M., Mazandu G.K., Ederveen T.H.A., Mulder N., Chimusa E., and Hoen P., 2022, Computational approaches for network-based integrative multi-omics analysis, Frontiers in Molecular Biosciences, 9: 967205.
https://doi.org/10.3389/fmolb.2022.967205

Augustyn D.R., Wyciślik Ł., and Mrozek D., 2021, Perspectives of using cloud computing in integrative analysis of multi-omics data, Briefings in Functional Genomics, 20(4): 198-206.
https://doi.org/10.1093/bfgp/elab007

Benincasa G., Demeo D.L., Glass K., Silverman E., and Napoli C., 2020, Epigenetics and pulmonary diseases in the horizon of precision medicine: a review, European Respiratory Journal, 57(6).
https://doi.org/10.1183/13993003.03406-2020

Bhattacharya A., Li Y., and Love M.I., 2020, Mostwas: multi-omic strategies for transcriptome-wide association studies, PLoS Genetics, 17(3): e1009398.
https://doi.org/10.1101/2020.04.17.047225

Blum B., Mousavi F., and Emili A., 2018, Single-platform 'multi-omic' profiling: unified mass spectrometry and computational workflows for integrative proteomics-metabolomics analysis, Molecular Omics, 14(5): 307-319.
https://doi.org/10.1039/c8mo00136g

Campbell P., Getz G., Stuart J., Korbel J., Stein L., and I., 2020, Pan-cancer analysis of whole genomes, Nature, 578: 82-93.
https://doi.org/10.1038/s41586-020-1969-6

Demirel H.C., Arici M.K., and Tuncbag N., 2021, Computational approaches leveraging integrated connections of multi-omic data toward clinical applications, Molecular Omics, 18(1): 7-18.
https://doi.org/10.1039/d1mo00158b

Ding D.Y., 2024, The role and challenges of genome-wide association studies in revealing crop genetic diversity, Bioscience Method, 14(1): 8-19.
https://doi.org/10.5376/bm.2024.15.0002

Durek P., Nordström K., Gasparoni G., Salhab A., Kressler C., Almeida M., Bassler K., Ulas T., Schmidt F., Xiong J., Glažar P., Klironomos F., Sinha A., Kinkley S., Yang X., Arrigoni L., Amirabad A., Ardakani F., Feuerbach L., Gorka O., Ebert P., Müller F., Li N., Frischbutter S., Schlickeiser S., Cendón C., Fröhler S., Felder B., Gasparoni N., Imbusch C., Hutter B., Zipprich G., Tauchmann Y., Reinke S., Wassilew G., Hoffmann U., Richter A., Sieverling L., Chang H., Syrbe U., Kalus U., Eils J., Brors B., Manke T., Ruland J., Lengauer T., Rajewsky N., Chen W., Dong J., Sawitzki B., Chung H., Rosenstiel P., Schulz M., Schultze J., Radbruch A., Walter J., Hamann A., and Polansky J., 2016, Epigenomic profiling of human CD4+ T cells supports a linear differentiation model and highlights molecular regulators of memory development, Immunity, 45(5): 1148-1161.
https://doi.org/10.1016/j.immuni.2016.10.022

Duruflé H., Selmani M., Ranocha P., Jamet E., Dunand C., and Déjean S., 2020, A powerful framework for an integrative study with heterogeneous omics data: from univariate statistics to multi-block analysis, Briefings in Bioinformatics, 22(3): bbaa166.
https://doi.org/10.1093/bib/bbaa166

Gopi L.K., and Kidder B.L., 2021, Integrative pan cancer analysis reveals epigenomic variation in cancer type and cell specific chromatin domains, Nature Communications, 12(1): 1419.
https://doi.org/10.1038/s41467-021-21707-1

Gusev A., Ko A., Shi H., Bhatia G., Chung W., Penninx B., Jansen R., Geus E., Boomsma D., Wright F., Sullivan P., Nikkola E., Alvarez M., Civelek M., Lusis A., Lehtimäki T., Raitoharju E., Kähönen M., Seppälä I., Raitakari O., Kuusisto J., Laakso M., Price A., Pajukanta P., and Pasaniuc B., 2015, Integrative approaches for large-scale transcriptome-wide association studies, Nature Genetics, 48: 245-252.
https://doi.org/10.1101/024083

Jiménez-Jiménez V., Martí-Gómez C., Pozo M.A., Lara-Pezzi E., and Sánchez-Cabo F., 2021, Bayesian inference of gene expression, Bioinformatics, 2021: 65-87.
https://doi.org/10.36255/EXONPUBLICATIONS.BIOINFORMATICS.2021.CH5

Karczewski K., and Snyder M., 2018, Integrative omics for health and disease, Nature Reviews Genetics, 19: 299-310.
https://doi.org/10.1038/nrg.2018.4

Knoch D., Meyer R.C., Heuermann M.C., Riewe D., Peleke F.F., Szymański J., Abbadi A., Snowdon R., and Altmann T., 2023, Integrated multi-omics analyses and genome-wide association studies reveal prime candidate genes of metabolic and vegetative growth variation in canola, The Plant Journal: For Cell and Molecular Biology, 117(3): 713-728.
https://doi.org/10.1111/tpj.16524

Kulis M., and Martín-Subero J., 2022, Integrative epigenomics in chronic lymphocytic leukaemia: Biological insights and clinical applications, British Journal of Haematology, 200: 280-290.
https://doi.org/10.1111/bjh.18465

Kumar D., Bansal G., Narang A., Basak T., Abbas T., and Dash D., 2016, Integrating transcriptome and proteome profiling: strategies and applications, Proteomics, 16(19): 2533-2544.
https://doi.org/10.1002/pmic.201600140

Mason J., 2024 Multiplex immunofluorescence in colorectal cancer: a retrospective analysis from scot and quasar 2 trials, Cancer Genetics and Epigenetics, 12(1): 66-69.
https://doi.org/10.5376/cge.2024.12.0008

Nalbantoğlu S., and Karadag A., 2021, Metabolomics bridging proteomics along metabolites/oncometabolites and protein modifications: paving the way toward integrative multiomics, Journal of Pharmaceutical and Biomedical Analysis, 199: 114031.
https://doi.org/10.1016/j.jpba.2021.114031

Qin J., Yan B., Hu Y.H., Wang P.W., and Wang J.W., 2016, Applications of integrative OMICs approaches to gene regulation studies, Quantitative Biology, 4(4): 283-301.
https://doi.org/10.1007/s40484-016-0085-y

Randhawa V., and Pathania S., 2020, Advancing from protein interactomes and gene co-expression networks towards multi-omics-based composite networks: approaches for predicting and extracting biological knowledge, Briefings in Functional Genomics, 19(5-6): 364-376.
https://doi.org/10.1093/bfgp/elaa015

Reel P.S., Reel S., Pearson E., Trucco E., and Jefferson E., 2021, Using machine learning approaches for multi-omics data analysis: a review, Biotechnology Advances, 49: 107739.
https://doi.org/10.1016/j.biotechadv.2021.107739

Stuart T., and Satija R., 2019, Integrative single-cell analysis, Nature Reviews Genetics, 20: 257-272.
https://doi.org/10.1038/s41576-019-0093-7

Subramanian I., Verma S., Kumar S., Jere A., and Anamika K., 2020, Multi-omics Data Integration Interpretation and Its application, Bioinformatics and Biology Insights, 14: 1177932219899051.
https://doi.org/10.1177/1177932219899051

Sun Y.V., and Hu Y.J., 2016, Integrative analysis of multi-omics data for discovery and functional studies of complex human diseases, Advances in Genetics, 93: 147-190.
https://doi.org/10.1016/bs.adgen.2015.11.004

Teschendorff A., and Relton C., 2017, Statistical and integrative system-level analysis of DNA methylation data, Nature Reviews Genetics, 19: 129-147.
https://doi.org/10.1038/nrg.2017.86

Wang X.C., 2019, Protein and proteome atlas for plants under stresses: new highlights and ways for integrated omics in post-genomics era, International Journal of Molecular Sciences, 20(20): 5222.
https://doi.org/10.3390/ijms20205222

Wörheide M., Krumsiek J., Kastenmüller G., and Arnold M., 2021, Multi-omics integration in biomedical research - A metabolomics-centric review, Analytica Chimica Acta, 1141: 144-162.
https://doi.org/10.1016/j.aca.2020.10.038

Yang J., Fritsche L., Zhou X., and Abecasis G., 2017, A scalable bayesian method for integrating functional information in genome-wide association studies, American Journal of Human Genetics, 101(3): 404-416.
https://doi.org/10.1016/j.ajhg.2017.08.002

Yang Y., Saand M.A., Huang L., Abdelaal W.B., Zhang J., Wu Y., Li J., Sirohi M.H., and Wang F., 2021, Applications of multi-omics technologies for crop improvement, Frontiers in Plant Science, 12: 563953.
https://doi.org/10.3389/fpls.2021.563953

Zhu C., Zhang Y., Li Y.E., Lucero J., Behrens M.M., and Ren B., 2021, Joint profiling of histone modifications and transcriptome in single cells from mouse brain, Nature Methods, 18(3): 283-292.
https://doi.org/10.1038/s41592-021-01060-3